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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Banerjee, *et al.*

Serial No.: 09/887,281

Confirmation No.: 6268

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For: *BRONCHODILATING COMPOSITIONS AND METHODS*

Art Unit: 1614

Examiner: Weddington, K.

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SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN ACCORDANCE WITH 37 C.F.R. §§ 1.97-1.98

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Dear Sir:

Since this Supplemental Information Disclosure Statement is filed together with a Request for Continued Examination of the above-captioned application, no fee should be due. If it is determined that a fee is due and no proper payment is enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-1213.

In accordance with the duty of disclosure imposed by 37 C.F.R. §1.56 to inform the Patent Office of all information known by Applicant or Applicant's representative that may be material to the examination of the subject application, Applicant's representative hereby provides this Supplemental Information Disclosure Statement that is prepared in accordance with 37 C.F.R. §§1.97-1.98. A copy of the Office Action in co-owned U.S. Application Serial No. 09/887,496, mailed May 20, 2003, is enclosed for the Examiner's review.

Office Action in 09/887,496

An Office Action in co-owned U.S. Application Serial No. 09/887,496, mailed May 20, 2003, and made final, rejects claims 1-64, 69-83, 87-89, 99-112 and 117-119 under 35 U.S.C. §103(a) as allegedly being unpatentable over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the Physician's Desk Reference (PDR) entry for fluticasone propionate. Claim 1 of 09/887,496 is representative of the rejected claims:

> 1. A pharmaceutical composition, comprising (i) formoterol, or a derivative thereof; and (ii)a steroidal anti-inflammatory agent, or a derivative thereof;
>
> in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Claim 93 is rejected as allegedly being obvious over the above references and further in view of the PDR entires for albuterol, accolate and Zyflo. Claim 93 is directed to the composition of claim 1, further containing one or more of a β2-adrenoreceptor agonist; a dopamine (D2) receptor agonist; an IL-5 inhibitor; an antisense modulator of IL-5; a tryptase inhibitor; a tachykinin receptor antagonist; milrinone or milrinone lactate; a leukotriene receptor antagonist; a 5-lypoxygenase inhibitor; or an anit-IgE antibody.

Claims 113-116, insofar as they read on ipratropium bromide, are rejected as allegedly being obvious over Hochrainer *et al.*, Bartow *et al.* and the PDR, as above, and further in view of Hardman *et al.* (*Goodman Gilman's The Pharmacological Basis of Therapeutics*, 1996, page 665). Claim 113 is representative of these claims, and is directed to the composition of claim 1 further containing an anticholinergic agent.

Claims 113-116, insofar as they read on tiotropium bromide, are rejected as allegedly being obvious over Hochrainer *et al.*, Bartow *et al.* and the PDR, as above, and further in view of Leckie *et al.* (*Novel Therapy of COPD*, abstract, January 2000).

Hochrainer *et al.*

Applicant had previously argued, *inter alia*, that Hochrainer *et al.* teaches two compositions: 1) an "active substance concentrate;" and 2) a "pharmaceutical preparation."

"Active substance concentrate"

The "active substance concentrate" is not formulated at a concentration for direct administration to a subject in need thereof. The "active substance concentrate" is taught as a "highly concentrated" solution or suspension (*i.e.*, greater than 10 mg/mL, preferably 75 to 500 mg/mL) that is stable for a period of several months, possibly up to several years without any deterioration in the pharmaceutical quality (see, *e.g.*, column 1, lines 55-61; column 2, lines 4-7; and claim 1 of Hochrainer *et al.*). The "highly concentrated" "active substance concentrate" of the reference is not suitable for direct administration to a subject in need thereof. See, *e.g.*, column 2, lines 1-4:

> The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted.

See also, *e.g.*, column 1, lines 47-52:

> The active substance concentrate according to the invention may be converted, by diluting with a pharmacologically acceptable liquid which optionally contains pharmaceutical adjuvants and additives, into a pharmaceutical preparation (aerosol formulation) which is converted by means of a nebulizer into an inhalabel aerosol.

See also, *e.g.*, column 4, lines 9-13:

> The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

Thus the "active substance concentrate" of Hochrainer *et al.* is merely a means for the storage of highly concentrated solutions of formoterol, ans is not formulated at a concentration for direct administration to a subject in need thereof.

"Pharmaceutical preparation"

Furthermore, Applicant argued that Hochrainer *et al.* teaches that formoterol

compositions formulated at a concentration for direct administration to a subject in need thereof are not stable, and therefore the reference teaches away from the claimed subject matter. Applicant pointed to column 1, lines 30-35, where the reference teaches:

> In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since *formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.* (emphasis added)

In response to Applicant's arguments, Examiner Mojdeh Bahar stated "[n]ote that nowhere does Hochrainer teach that its composition suitable for direct administration is unstable." The Examiner also stated "[n]ote that [the] quotation [above] merely reports what was known in the art prior to the Hochrainer patent and cannot be construed to mean that the Hochrainer pharmaceutical composition itself will be unstable." Applicant respectfully disagrees with the Examiner Bahar's characterization of the teachings of Hochrainer *et al.*

The above-referenced quotation from Hochrainer *et al.* states more that the prior art knowledge. It states unequivocally that formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time. This is not stated merely in the context of prior compositions, but rather is stated as an alleged property of formoterol itself. Therefore, Hochrainer *et al.* teaches away from the subject matter claimed in 09/887,496.

Moreover, Hochrainer *et al.* states in Example 3 (column 6, lines 55-59) that an aqueous solution of formoterol at pH 5.0 is not stable during long term storage (only 10% remaining after 3 months at 40 °C). This solution corresponds to the pharmaceutical preparations of Examples 1 and 2 of Hochrainer *et al.* The reference further teaches in Example 3 that a comparable suspension is stable for 6 months at 40 °C. This suspension is comparable to the active substance concentrates of Examples 1 and 2 of the reference. Therefore, Hochrainer *et al.* does teach in Example 3 that its "pharmaceutical preparation" is unstable during

long term storage, and the claims of 09/887,496 are not obvious over the teachings of Hochrainer *et al.* and the cited secondary references.

The instant claims (of U.S. Application Serial No. 09/887,281)

Instant claim 1 is representative of the subject matter claimed in the instant application (09/887,281):

> 1. A pharmaceutical composition, comprising formoterol, or a derivative thereof;
> in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof.

As described in detail above, Hochrainer *et al.* does not teach or suggest any aqueous compositions containing formoterol that are stable during long term storage and are formulated at a concentration suitable for direct administration to a subject in need thereof. Therefore, the instant claims are not obvious over the teachings of Hochrainer *et al.*

Although this information is made known to the Patent and Trademark Office in compliance with Applicant's duty of disclosure, such disclosure is not to be construed as an admission by Applicant or Applicant's representative that the references cited in the Office Action for 09/887,496 are effective as prior art against the subject application. In accordance with 37 C.F.R. §1.97(h), the filing of this Supplemental Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. §1.56(b) exists.

* * *

Applicant respectfully requests that the Examiner review the foregoing information and that it be made of record in the file history of the above-captioned application. In view of the above, Applicant respectfully requests allowance of the application.

Respectfully submitted,
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